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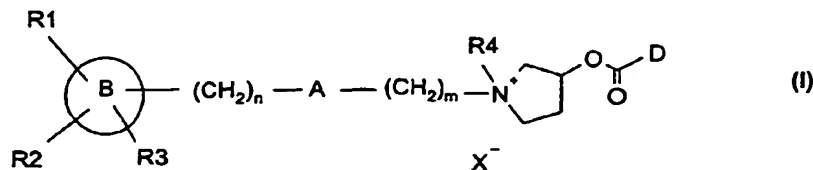
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200200889 16 April 2002 (16.04.2002) ES
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(54) Title: PYRROLIDINIUM DERIVATIVES AS ANTAGONISTS OF M3 MUSCARINIC RECEPTORS



(57) Abstract: New pyrrolidinium derivatives having the chemical structure of general formula (I) are disclosed; as well as processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as antagonists of M3 muscarinic receptors.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03786

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/14 C07D 12 C07D207/12 C07D409/04 K31/4025  
 A61K31/40 A61P15/10 A61P11/00 A61P1/00 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 956 062 A (LUNSFORD CARL D) 11 October 1960 (1960-10-11) cited in the application column 4, line 34; example 1 column 5, line 2; example 3 examples 19,24,31; table I column 8, line 7,8 column 2, line 5	1,20,21, 28
X	US 3 301 869 A (LUNSFORD CARL D) 31 January 1967 (1967-01-31) column 1, line 67 - line 72 example 14; table X	1,20,21, 28

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
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Date of the actual completion of the international search

15 January 2004

Date of mailing of the international search report

30. 01. 2004

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## INTERNATIONAL SEARCH REPORT

In International Application No

PCT/EP 03/03786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  OGINO, YOSHIO ET AL: "Preparation of  2-aryl-2-hydroxyacetic acid ester  derivatives as muscarinic M3 receptor  antagonists"  retrieved from STN  Database accession no. 136:118468  XP002222161  CAS RN: 389888-86-2; 389890-38-4  abstract  &amp; WO 02 004402 A (BANYU PHARMACEUTICAL  CO., LTD., JAPAN)  17 January 2002 (2002-01-17)  -&amp; EP 1 302 458 A (BANYU PHARMA CO LTD)  16 April 2003 (2003-04-16)  claim 1</p>	1,28
X	<p>FR 2 155 927 A (SYNTHELABO)  25 May 1973 (1973-05-25)  example 11  page 1, line 9,10  page 16, line 25 - line 31</p>	1,21,28
Y	<p>EP 0 863 141 A (BANYU PHARMA CO LTD)  9 September 1998 (1998-09-09)  example 13  claims 1,5,6</p>	1,28
Y	<p>US 3 714 357 A (GUEREMY C ET AL)  30 January 1973 (1973-01-30)  examples 1,11-18  column 15</p>	1,28
Y	<p>WO 01 04118 A (ALMIRALL PRODESFARMA SA  ;BUIL ALBERO MARIA ANTONIA (ES);  FERNANDEZ) 18 January 2001 (2001-01-18)  claims 1,34,35</p>	1,28
Y	<p>FRANKO B V ET AL: "DERIVATIVES OF  3-PYRROLIDINOLS-III. THE CHEMISTRY,  PHARMACOLOGY, AND TOXICOLOGY OF SOME  N-SUBSTITUTED-3-PYRROLIDYL  ALPHA-SUBSTITUTED PHENYLACETATES"  JOURNAL OF MEDICINAL AND PHARMACEUTICAL  CHEMISTRY, AMERICAN CHEMICAL SOCIETY,  EASTON, US,  vol. 2, no. 5, 1960, pages 523-540,  XP008021298  page 534 -page 539  examples 235,282,340,479,362,346,349,343</p>	1,28
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03786

## C.(Continuation) DOCUMENTS CONSIDERED MORE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 005, no. 148 (C-072), 18 September 1981 (1981-09-18) -& JP 56 079688 A (OTA SEIYAKU KK), 30 June 1981 (1981-06-30) abstract page 642	1,28
A	WO 98 21183 A (NOE CHRISTIAN R ;WELBROECK MAGALI (BE); LAMBRECHT GUENTER (DE); C) 22 May 1998 (1998-05-22) claims 17,18; example 1	1,28

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/JP 03/03786

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,12-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents phenyl or biphenyl and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, their pharmaceutical use according to claims 26-33 and the intermediates  
2-hydroxy-2,2-dithien-2-ylacetic acid  
(3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester,  
2-hydroxy-2,2-dithien-2-ylacetic acid  
(3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester,  
2-hydroxy-2,2-dithien-2-ylacetic acid  
(3R)-1-phenethylpyrrolidin-3-yl ester of claim 23 and  
(3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol of claim 24.

2. Claims: 1-9,11-14,17-22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents phenyl or biphenyl and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

3. Claims: 1,2,4-7,10,12-18,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents naphthalenyl or 5,6,7,8-tetrahydronaphthalenyl and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

4. Claims: 1,2,4-7,11-14,17,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents naphthalenyl or 5,6,7,8-tetrahydronaphthalenyl and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

5. Claims: 1-10,12-33(all partially)

Compounds according to formula (I) of claim 1 in which B represents benzo[1,3]dioxolyl or a heteroaromatic group and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, their pharmaceutical use according to claims 26-33 and the

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 03 03786

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

intermediates 2-hydroxy-2,2-dithien-2-ylacetic acid  
(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of claim 23  
and (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol of claim 24

6. Claims: 1-9,11-14,17,18,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents benzo[1,3]dioxolyl or a heteroaromatic group and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

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In: International Application No

PCT/EP 03/03786

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